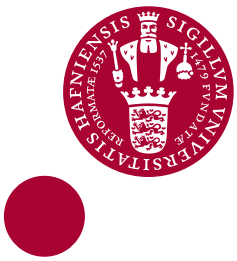

Safety of dried aerial parts of Hoodia parviflora as a novel food pursuant to Regulation (EC) No 258/97

(Scientific Opinion)

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

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Safety of dried aerial parts of *Hoodia parviflora* as a novel food pursuant to Regulation (EC) No 258/97

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Abstract

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the dried aerial parts of *Hoodia parviflora* as a novel food (NF) submitted pursuant to Regulation (EC) No 258/97. The information provided on the composition, the specifications, the production process, the batch-to-batch variability and the stability of the NF is sufficient and does not raise safety concerns. The applicant intends to use the NF in a number of energy-reduced/sugar-free/no-added-sugar foods in quantities of up to 15 mg per serving. The applicant also proposes to provide the NF as a food supplement. The target population proposed by the applicant is adults. The highest intake estimates were found in the group of elderly (≥ 65 years) individuals, with a high intake of 1.0 mg/kg body weight (bw) per day. One 90-day toxicity study in rodents was provided from which a benchmark dose lower confidence limit ($BMDL_{05}$) of 53.5 mg/kg bw per day was derived for effects of the NF on bodyweight. The Panel concludes that the addition of the NF to foods as a food ingredient at the uses and use levels as proposed by the applicant would exceed intake levels considered safe in humans. The Panel considers that the NF is safe to be used as a food supplement at a maximum dose of 9.4 mg/day. The target population is adults.

Keywords: *Hoodia parviflora*, dried aerial parts, novel food, safety

Requestor: European Commission following an application by Desert Labs Ltd.

Question number: EFSA-Q-2016-00091

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Summary

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on dried aerial parts of *Hoodia parviflora* as a novel food (NF) pursuant to Regulation (EC) No 258/97. The assessment follows the methodology set in Commission Recommendation 97/618/EC. The assessment is based on the data supplied in the original application, the initial assessment by the competent authority of Ireland, the concerns and objections of a scientific nature of the other Member States and the responses of the applicant.

The NF is the whole dried aerial parts of *Hoodia parviflora*, which is a succulent cactus-like milkweed plant native to southern Africa. The raw material, which is harvested from plants of more than 3 years, is sanitised, freeze-dried and ground into a fine powder.

The information provided on the composition, the specifications, batch-to-batch variability, the production process and the stability of the NF is sufficient and does not raise safety concerns.

The applicant intends to use the NF in a number of energy-reduced/sugar-free/no-added-sugar foods in quantities of up to 15 mg per serving. The applicant also proposes to provide the NF as a food supplement, with a recommended daily dose of up to 40 mg/day. The target population proposed by the applicant is adults.

When estimating intakes of the NF from the foods intended to be fortified, the highest intakes were found for elderly (≥ 65 years) individuals, with mean and high (95th percentile) intakes of 0.3 and 1.0 mg/kg body weight (bw) per day, respectively.

Based on the genotoxicity tests provided, the Panel concludes that there are no concerns regarding genotoxicity of the NF.

No conclusions could be drawn from the two human studies provided, owing to methodological weaknesses.

The risk of allergic reactions to the NF is low.

One 90-day repeated dose oral toxicity study was provided with the NF, which was administered to rodents at dosages of 100, 250 and 350 mg/kg bw per day. When the data from the study were subjected to benchmark dose (BMD) modelling, a BMD lower confidence limit ($BMDL_{05}$) of 53.5 mg/kg bw per day (for the endpoint body weight) was derived, which is considered by the Panel as the reference point.

Considering the $BMDL_{05}$ of 53.5 mg/kg bw per day, and the estimated high intakes of the NF from fortified foods of 1.0 mg/kg bw per day, the resulting margin of exposure (MoE) is 53.5. With regard to food supplements and the proposed maximum daily intake of the NF, the resulting MoE is 94. The Panel considers these MoEs for fortified foods and food supplements as insufficient.

Considering the $BMDL_{05}$ of 53.5 mg/kg bw per day and by applying an uncertainty factor of 400 (composed of a factor of 100 to account for inter- and intra-species variability plus a factor of 4 to account for uncertainty for the content of the hoodigosides tested in the subchronic toxicity study), the Panel considers an intake of 0.134 mg/kg bw per day of the NF in the form of food supplements as safe. In adults (i.e. the target population) with a default body weight of 70 kg, this intake level corresponds to a maximum daily dose of 9.4 mg.

The Panel concludes that the addition of the NF, dried aerial parts of *Hoodia parviflora*, to foods as a food ingredient at the uses and use levels as proposed by the applicant would exceed intake levels considered safe in humans.

The Panel considers that the NF is safe to be used as a food supplement at a maximum daily dose of 9.4 mg. The target population is adults.

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

On 13 February 2015, the company Desert Labs, Ltd of Israel submitted a request in accordance with Article 4 of the Novel Food Regulation (EC) No 258/97[1] to place on the market dried aerial parts of *Hoodia parviflora* as a novel food (NF) ingredient.

On 24 August 2015, the competent authority of Ireland forwarded to the Commission its initial assessment report, which came to the conclusion that dried aerial parts of *Hoodia parviflora* meet the criteria for acceptance of a NF defined in Article (3)1 of Regulation (EC) No 258/97.

On 24 August 2015, the Commission forwarded the initial assessment report to the other Member States (MS). Several MS submitted comments or raised objections.

The concerns of a scientific nature raised by the MS can be summarised as follows:

- A number of MS questioned the no-observed-adverse-effect-level (NOAEL) as derived by the applicant. The MS argued that the reductions in body weight, body weight gain and food consumption observed in females receiving the mid- and high-dose and the reduced food consumption in males receiving the high dose in the repeated dose toxicity study should be considered as adverse effects, rather than as an intended weight loss effect as claimed by the applicant. In particular, since the mode of action of the food is largely unknown.
- Some MS requested more information on the mechanism by which the food could have an effect on body weight and/or appetite.
- One MS criticised that the concentration of hoodigosides in the product used in the 90-day subchronic toxicity study was less than the maximum concentration as indicated in the specifications.
- The specification for total glycosides is very broad, as is the range for the total sugar content.
- The parameters of the proximate analysis should be included in the specifications.
- According to the description of the manufacturing process, peroxyacetic acid and sodium dichloroisocyanurate are used as processing aids for disinfection of the aerial parts of *Hoodia parviflora*. Documentation should be submitted to demonstrate that no residues, or only unintentional but technically unavoidable residues of the substances or their derivatives, are present in the final product, and that these do not present any health risk and do not have any technological effect on the final product.
- Previous data on components from *Hoodia gordonii* in the scientific literature should be considered for the evaluation.
- Some MS commented on the limited information provided for the stability of the NF.
- The human study by Landor et al. (2015) was performed with daily doses of the NF which are lower than the expected intake of the NF. Plus the study duration is substantially shorter than the intake period of 6 months for adults, as proposed by the applicant.
- The carbohydrate content of the food should be characterised in more detail.
- With respect to allergenicity of the NF, one MS requested a taxonomical analysis of the NF compared to known allergens to allow a more detailed categorisation of the plant. Another MS noted that the NF contains a fair amount of proteins and that these proteins have not been characterised nor the molecular weight distribution of the protein fraction analysed. Such information would help assess the allergy potential of the NF preparation.
- One MS commented that the provided dietary intake estimates were based on the UK Food Consumption Survey (NDNS) and that national consumption data should be addressed with care when extrapolating national data to other MS.
- The number of foods to which the NF is added should be limited, e.g. by excluding confectionery, biscuits and snacks, in order to reduce the likelihood of excessive consumption.

[1] Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. OJ L 43, 14.2.1997, p. 1–6.

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002[2], the European Food Safety Authority (EFSA) is asked to carry out the additional assessment for dried aerial parts of *Hoodia parviflora* as a NF in the context of Regulation (EC) No 258/97.

EFSA is asked to carry out the additional assessment and to consider the elements of a scientific nature in the comments raised by the other MS.

2. Data and methodologies

2.1. Data

The assessment of the safety of the NF is based on data supplied in the original application, the initial assessment by the competent authority of Ireland, the concerns and objections of a scientific nature of the other MS and the responses of the applicant.

In accordance with Commission Recommendation 97/618/EC[3], the NF, the dried aerial parts of *Hoodia parviflora*, is allocated to Class 2.2, i.e. complex NF from a non-genetically modified (non-GM) source; the source of the NF has no history of food use in the Community. The data are required to comply with the information required for NFs of Class 2.2, i.e. structured schemes I, II, III, IX, XI, XII and XIII of Commission Recommendation 97/618/EC. In the current opinion, these structured schemes are listed in Sections 3.1–3.8. The intention is to use the NF as an ingredient in a number of energy-reduced/sugar-free/no-added-sugar foods. The NF is also intended for use in food supplements. This assessment concerns only risks that might be associated with consumption of the NF at the proposed conditions of use and is not an assessment of the efficacy of dried aerial parts of *Hoodia parviflora* with regard to any claimed benefit.

2.2. Methodologies

The assessment follows the methodology set out in Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of NFs and NF ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council.

3. Assessment

3.1. Specification of the Novel Food

The NF is the whole dried aerial parts of *Hoodia parviflora*, which is a succulent cactus-like milkweed plant of the Apocynaceae family native to southern Africa. The NF, i.e. the dried crude biomass of *H. parviflora*, is described as a bitter-tasting light green to tan fine powder with less than 5% moisture content.

The NF consists primarily of carbohydrates (70–80%), more than half of which is dietary fibre (resulting in a fibre content of the NF of 45–54%), protein (2.5–4.5%) and fat (1.5–3%).

The applicant also provided analyses of micronutrients, including vitamins and minerals, the fatty acid profile and the content of the major hoodigosides (i.e. hoodigosides P57, O and L) in the NF, as measured on a dry weight basis by ultra-performance liquid chromatography/mass spectrometry (UPLC/MS) and liquid chromatography with tandem mass spectrometry (LC–MS/MS) (adapted from Avula et al., 2008).

The specifications for the NF have been provided (Table 1) and include physical and chemical parameters as well as specifications for contaminants such as heavy metals and selected microorganisms.

[2] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

[3] Commission Recommendation 97/618/EC: Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council. OJ L 253, 16.9.1997, p. 1–36.

Table 1: Specifications of the NF

Parameter	Specification	Method
Plant material	Aerial parts of at least 3-year-old plants	Planting recorded and mapped
Appearance	Light green to tan fine powder	Visual
Flavour	bitter	Tasting
Solubility (mg/mL water)	> 25	By titration
Moisture (%)	< 5.5	Karl Fischer; AOCS Ca 2e-84
A_w	< 0.3	NCFA No. 168
pH	< 5.0	EPA 150.1
Odour	Slightly plant-like	Smelling
Mesh, μ	> 20	Sieving
Protein (g/100 g)	< 4.5	Combustion; in house procedure F = 6.25
Fat (g/100 g)	< 3	By hydrolysis; validated in house method LI 00.527-1
Carbohydrate (g/100 g)	< 80	By calculation
Dietary fibre (g/100 g)	< 55	AOAC 991.43
Total sugars (g/100 g)	< 10.5	Validated in house method LI 00.544-2
Ash (%)	< 20	AOAC 942.05
Hoodigosides		
P57 (mg/kg)	5–50	UPLC/MS[(a)] LC–MS/MS[(a)]
L (mg/kg)	1,000–6,000	
O (mg/kg)	500–5,000	
Total (mg/kg)	1,500–11,000	
Contaminants		
Arsenic (mg/kg)	< 1.00	MWD-ICP-MS
Mercury (mg/kg)	< 0.1	
Cadmium (mg/kg)	< 0.1	
Lead (mg/kg)	< 0.5	
Microbial		
Aerobic plate count (CFU/g)	< 10^5	SI 885 part 3
Escherichia coli (CFU/g)	< 10	SI 885 part 12
Staphylococcus aureus (CFU/g)	< 50	SI 885 part 6
Total coliforms (CFU/g)	< 10	SI 885 part 4
Yeast (CFU/g)	≤ 100	SI 885 part 8
Mould (CFU/g)	≤ 100	SI 885 part 8
Salmonella species (CFU/25 g)	Negative	SI 885 part 7; FDA BAM
Listeria monocytogenes (CFU/25 g)	negative	MFHPB-30; CMMEF chapter 38

AOAC: Association Of Analytical Communities; BAM: Bacteriological Analytical Manual; CFU: colony forming units; UPLC/MS: ultra-performance liquid chromatography/mass spectrometry; AOCS: American Oil Chemists' Society; CMMEF: Compendium of Methods for the Microbiological Examination of Foods; FDA BAM: Food and Drug Administration Bacteriological Analytical Manual; LC–MS/MS: liquid chromatography tandem mass spectrometry; MGHPB: Health Products and Food Branch of Health Canada methods for the microbiological analysis of foods; MWD-ICP-MS: multiple wavelength detector-inductively coupled plasma-mass spectrometry; NCFA: Nordic Committee on Food Analysis; SI: Standards of Israel; EPA: Environmental Protection Agency.

(a): Methods adapted from Avula et al. (2008) by Phytochemical Services Incorporated (PSL), National Center for Natural Products Research (NCNPR) University of Mississippi.

The applicant provided batch-to-batch analyses (Table 2) for three non-consecutive batches of the NF in order to confirm that the manufacturing process is reproducible and adequate to produce a product that is within the specifications as set above. Information on the microbiological status of the NF was provided for the three batches plus two additional batches.

Table 2: Batch-to batch analyses of the NF

Parameter	Specification	Batch results				
		Pm34901[(a)]	P22601	P02901	P18001	P05701
Plant material	Aerial parts of at least 3-year-old plants	November 2007	November 2008	November 2008	–	–
Appearance	Light green to tan fine powder	Complies	Complies	Complies	–	–
Flavour	Bitter	Complies	Complies	Complies	–	–
Solubility (mg/mL water)	> 25	50	na	28.8	–	–
Moisture (%)	< 5.5	5.18	1.27	5.66	–	–
A_w	< 0.3	na	na	<0.3	–	–
pH	≤ 5.0	4.6	4.5	4.31	–	–
Odour	Slightly plant-like	Complies	Complies	Complies	–	–
Mesh, μ	> 20	Complies	Complies	Complies	–	–
Protein (g/100 g)	< 4.5	4.45	3.53	3.4	–	–
Fat (g/100 g)	< 3	4.55[(b)]	2.16	1.07	–	–
Carbohydrate (g/100 g)	< 80	71.15	76.51	75.2	–	–
Dietary fibre (g/100 g)	< 55	45.5	50.1	53.3	–	–
Total sugars (g/100 g)	< 10.5	12.87[(b)]	5.5	6.5	–	–
Ash (%)	< 20	17.61	16.53	14.67	–	–
Hoodigosides						
P57 (mg/kg)	5–50	16	30	14	–	–
L (mg/kg)	1,000–6,000	1,870	4,400	2,740	–	–
O (mg/kg)	500–5,000	640	3,200	1,450	–	–
Total (mg/kg)	1,500–11,000	2,530	7,630	4,200	–	–
Contaminants						
Arsenic (mg/kg)	< 1.0	0.09	< 0.1	< 0.1	–	–
Mercury (mg/kg)	< 0.1	0.012	< 0.02	< 0.02	–	–
Cadmium (mg/kg)	< 0.1	0.036	< 0.03	< 0.05	–	–
Lead (mg/kg)	< 0.5	0.07	< 0.1	< 0.1	–	–
Microbiological specifications						
Aerobic plate count (CFU/g)	< 10^5	200	600	140	< 1,000	50
Escherichia coli (CFU/g)	< 10	< 10	< 10	< 10	< 10	< 10
Staphylococcus coag. (CFU/g)	< 50	< 50	na	< 50	na	< 50
Total coliforms (CFU/g)	< 10	< 10	< 10	< 10	< 10	< 10
Yeast (CFU/g)	≤ 100	10	< 10	< 10	< 10	< 10
Mould (CFU/g)	≤ 100	< 10	< 10	< 10	< 10	< 10
Salmonella species (CFU/25 g)	Negative	na	Negative	Negative	Negative	Negative
Listeria monocytogenes (CFU/25 g)	Negative	Negative	Negative	Negative	Negative	Negative

CFU: colony forming units;
(a): Batch used for the toxicology tests; na: not available.
(b): The Panel notes that the values for fat and total sugars were above the upper limits as set in the specifications, which is not considered to be of safety concern.

The applicant routinely analyses the NF for pesticides and mycotoxins. Information was provided on the concentration of pesticides and a number of mycotoxins (i.e. aflatoxin B1; aflatoxin sum of B1, B2, G1, G2; ochratoxin; deoxynivalenol; fumonisins) in the NF.

The Panel considers that the information provided on the composition, the specifications and the batch-to-batch variability of the NF is sufficient and does not raise safety concerns.

3.1.1. Stability of the NF

The applicant provided the results of an ongoing (starting in 2013) 5-year stability study for one batch of the NF up to almost 3 years. The study was conducted at room temperature and humidity and the NF was stored in sealed aluminium bags (i.e. as suggested by the applicant for the ingredient to be marketed). The analyses indicate that the NF remains within specifications and is expected to remain stable under normal storage conditions for almost 3 years.

The Panel considers that the data provided sufficient information with respect to the stability of the NF.

3.2. Effect of the production process applied to the NF

The production of the NF is carried out according to current Good Manufacturing Practice (cGMP) standards with Hazard Analysis Critical Control Points (HACCP) controls in place.

The raw material used in the production of the NF is the aerial parts of *H. parviflora*, harvested from plants of more than 3 years of age, cultivated in the southern Arava region of Israel.

The manufacturing process begins by excising the aerial parts of *H. parviflora* plants. The plant parts are then sanitised in peroxyacetic acid and rinsed twice in tap water before being cut into pieces of 10–20 cm in size, freeze-dried and then ground into a powder. The powder is passed through a metal detector, packaged in double-sealed food grade bags and heat treated at 80°C for 6 h to ensure it meets microbiological specifications.

An overview of the manufacturing process has been provided.

Originally, the manufacturing process included the use of sodium dichloroisocyanurate in addition to/as an alternative to peroxyacetic acid. One MS requested documentation that no residues of the substances (or their derivatives) used during the manufacturing process are present in the final product and that these do not present any health risk and do not have any technological effect on the final product. In reply, the applicant communicated that the use of sodium dichloroisocyanurate will be discontinued. The applicant was requested to provide information on how it will be assured that after discontinuation of the use of sodium dichloroisocyanurate, the NF will still meet the microbiological specifications, considering that sodium dichloroisocyanurate was used as a processing aid for the disinfection of the NF. In reply, the applicant argued that peroxyacetic acid will be used as a disinfection agent instead and that, in addition, the dried aerial parts of *H. parviflora* will be heat treated at 80°C for 6 h in order to further ensure that the microbiological specifications are met. The applicant also pointed out that batches will continuously be monitored to ensure that the NF is compliant with the microbiological specifications.

With regard to peroxyacetic acid, the applicant argued that this acid is commonly used in food, beverages and dairy industry as antimicrobial at a concentration of 0.1–4.0% and is reported to be largely eliminated by washing. Antimicrobial solutions containing peroxyacetic acid have been evaluated by JECFA (2006), which concluded that such solutions do not pose a safety concern. The Panel considers that the acetic acid, which can be formed by hydrolysis of peroxyacetic acid, is of no health concern.

The Panel considers that the production process is sufficiently described and does not raise safety concerns.

3.3. History of the organism used as a source of the NF

The NF is manufactured from the aerial parts of *H. parviflora*, a cactus-like milkweed plant native to southern Africa. The taxonomic classification of *H. parviflora* is as follows: Kingdom: Plantae, Division: Tracheophyta, Class: Magnoliopsida, Order: Gentianales, Family: Apocynaceae, Genus: *Hoodia*, Species: *parviflora*.

Various *Hoodia* species (e.g. *H. pilifera*) have a history of food use by indigenous tribes of southern Africa.

3.4. Anticipated intake/extent of use of the NF

The applicant intends to use the NF as an ingredient in energy-reduced/sugar-free/no-added-sugar products at a maximum level of 15 mg per serving (proposed range 10–15 mg per serving) in the following foods: beverages (sugar-free fortified enhanced bottled water beverages and sugar-free fruit-flavoured powdered mixes), biscuits (health bars), confectionary (sugar-free hard and soft candies and sugar-free chewing gum), sweeteners (tabletop sweeteners), soups and broths (dehydrated vegetable soups), tea/coffee/water (herbal teas).

Serving sizes are based on the UK Food Portion Sizes handbook (FSA, 2002) and from manufacturers' websites.

The corresponding maximum concentrations of the NF in the respective foods are the following: bottled water beverages 2 mg/100 g (500 mL serving size), beverages powdered mixes 9.4 mg/100 g (160 mL serving size (reconstituted)), biscuits 37.5 mg/100 g (40 g serving size), sugar-free hard and soft candies 37.5 mg/100 g (40 g serving size), sugar-free chewing gum 750 mg/100 g (2 g serving size), tabletop sweeteners 1,000 mg/100 g (1 g serving size), soups and broths 6.8 mg/100 g (220 mL serving size (reconstituted)), herbal teas 5.3 mg/100 g (190 mL serving size (reconstituted)).

The applicant also intends to use the NF in food supplements at levels up to 40 mg/day (corresponding to 0.57 mg/kg body weight (bw) per day for an adult of 70 kg bw).

The target population for the NF is adults.

The applicant argues that the food supplements would be consumed as an alternative rather than in addition to foods fortified with the NF and proposes a labelling strategy to this end.

In order to estimate potential intakes from the proposed uses of the NF in the various foods, the applicant performed an intake assessment using food consumption data from the UK NDNS, 2008–2011 (UKDA, 2012). According to the applicant, this database (based on 4-day food diaries) was chosen since the proposed uses for the NF could be matched on a food-by-food basis allowing for a refined exposure assessment. However, only a limited number of food codes (e.g. sugar-free chewing gum) could be identified as sugar-free foods (i.e. foods to which the NF is intended to be added). Therefore, the applicant selected all food codes (for the proposed uses as indicated above) available in the UK NDNS 2008–2012 database as surrogate food codes in order to obtain a conservative intake estimate. For the statistical analysis and data management, Creme software (i.e. Creme Food 3.0) was used (Creme, 2013).

The applicant provided mean and high (i.e. 95% percentile (P95)) intake estimates based on the maximum proposed intake levels across the foods proposed for fortification with the NF for 'all-persons' (i.e. all individuals surveyed in the NDNS regardless of whether they would consume products that contain the NF) and for 'all-users' (i.e. consumers of the foods to which the NF is to be added).

Although the target population for the NF is the adult population, the applicant also included teenagers (from 12 years up) in the exposure assessment, as 'they could potentially consume the proposed foods'. Thus, the population groups considered for the intake estimates were female and male teenagers aged 12–18 years, female and male adults aged 19–64 years and the elderly (≥ 65 years).

Highest intake estimates were found for the group of the elderly, with mean and high (P95) intakes of 0.3 mg and 1.0 mg/kg bw per day, respectively (in the population of consumers). Female adults were found to have the second highest intakes with mean and high intakes of 0.2 mg and 0.7 mg/kg bw per day, respectively.

3.5. Information from previous human exposure to the NF or its source

The applicant has provided sales data for food supplements and various foods containing the NF for Israel, Japan, Russia and the USA for the years from 2009 to 2014. According to these data, by 2016, more than 15 million servings of the NF at levels up to 300 mg per serving have been sold. The applicant states that no adverse effects have been reported.

3.6. Nutritional information on the NF

Based on the information on the composition of the NF (Section 3.1, plus additional information on micronutrients provided by the applicant (not shown)) and the intended use levels (40 mg/day as food supplement; estimated mean and high intakes of 0.3 and 1.0 mg/kg bw per day, respectively, from fortified foods), the Panel considers that the NF is not nutritionally disadvantageous.

3.7. Microbiological information on the NF

The risk of microbiological contamination during the manufacturing process of the NF is minimised by a sanitation step, which is followed by freeze- or heat-drying, with ensuing heat sterilisation of the final product.

Microbiological specifications for the NF have been provided by the applicant and are indicated in Table 2 (Section 3.1). The microbiological status of the NF is supported by the results of five non-consecutive batches which were compliant with the specifications (Table 3, Section 3.1).

The Panel considers that the microbiological information provided does not raise safety concerns.

3.8. Toxicological information on the NF

In the publications and respective study reports, the batch of the NF which was tested was referred to as 'P2AC34811'. Upon request, the applicant clarified that this number represents the 'harvest' code, while the 'ingredient' code for this batch is Pm34901. The specifications for this batch have been provided (see Section 3.1, Table 2). The Panel notes that this tested batch contains an amount of only 2,530 mg/kg of total hoodigosides, which is more than four times lower than the maximum level of total hoodigosides of 11,000 mg/kg as set in the specifications. The Panel also notes that sources of hoodigosides are mentioned in the EFSA Compendium of botanicals, which lists botanicals that contain naturally occurring substances of possible concern for human health.[4]

3.8.1. Absorption, distribution, metabolism and excretion

The applicant did not provide studies on the absorption, distribution, metabolism and excretion (ADME) of the NF or any constituent therefrom.

3.8.2. Genotoxicity

The applicant provided the publication by Lynch et al. (2013a) who examined mutagenic potential of the NF in a bacterial reverse mutation test and an *in vitro* micronucleus test in accordance with the Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Scientific Committee, 2011).

The bacterial reverse mutation test (Lynch et al., 2013a) was conducted in compliance with OECD Test Guideline (TG) 471 (OECD, 1997). *Salmonella* Typhimurium strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2 uvrA were exposed to the test article by either the direct plate incorporation method or the pre-incubation method, in the presence or absence of an exogenous metabolic activation system (rat liver S9). Bacteria were incubated with the NF (Pm34901) at concentrations of 0 (distilled water control), 10.0, 31.6, 100, 316, 1,000, 2,500 or 5,000 μg/plate for 48 h. Precipitation of the test article was observed at concentrations of 316 μg/plate and greater, both in the presence and absence of metabolic activation. No cytotoxicity was observed in any test condition with the exception of a toxic effect observed in strain TA1537 at a concentration of 2,500 μg/plate in the absence of metabolic activation. No biologically relevant increases in revertant colony numbers of any of the five tested strains were observed following treatment with the NF at any concentration level, in the presence or absence of metabolic activation. Plates treated with the positive controls exhibited the expected increases in the numbers of revertant colonies.

The NF (Pm34901) was also assessed in an *in vitro* micronucleus assay with human lymphocytes (Lynch et al., 2013a) in accordance with OECD TG 487 (OECD, 2010) and Good Laboratory Practice (GLP). Precipitation of the test article was noted at concentrations of 100 μg/mL and higher, both in the presence and absence of metabolic activation. Based on the results of cytotoxicity measurements, doses for the main study were selected. In the short-term exposure, cells were incubated for 4 h with metabolic activation at concentrations of 1,500, 2,000 and 2,500 μg/mL and without metabolic activation at concentrations of 1,000, 1,500 and 2,000 μg/mL. In the long-term exposure, cells were exposed to the NF for 44 h in the absence of metabolic activation at concentrations of 250, 500 and 1,000 μg/mL. Approximately 2,000 binucleated cells per concentration were scored for micronuclei according to the criteria of Countryman and Heddle (1976). After short-term exposure and without metabolic activation, concentrations at 1,500 μg/mL and above were cytotoxic. In the presence of metabolic activation, no cytotoxicity was observed at the concentrations tested. The frequency of micronucleated cells observed in lymphocytes treated with the test article did not exhibit any statistically or biologically significant increases when compared to the negative control, in the absence and presence of metabolic activation, under short-term and long-term exposure conditions. Cells treated with the positive controls exhibited the expected increases in the frequency of micronucleated cells.

Based on the information provided, the Panel concludes that there are no concerns regarding genotoxicity of the NF.

[4] https://www.efsa.europa.eu/en/data/compendium-botanicals

3.8.3. Subacute and subchronic toxicity studies

The applicant submitted a 14-day dose-finding study (Desert Labs, 2012a) and a combined 90-day oral toxicity and reproductive and developmental toxicity study (Desert Labs, 2012b; Lynch et al., 2013b).

In the 14-day dose-finding study (Desert Labs, 2012a), Sprague–Dawley rats (5/sex per group) were administered via gavage 0, 100, 250, 500 and 750 mg/kg bw per day of the NF (batch No Pm34901). Statistically significant reductions in food consumption, body weight and body weight gain were observed in females in the 250, 500 and 750 mg/kg bw per day groups and in males in the 500 and 750 mg/kg bw per day groups. In gross necropsy, mottling of the kidney was observed in male and female rats after administration of 750 mg/kg bw per day of the test substance. No clinical chemistry, urinalysis or histopathology was performed in this dose-finding study.

The NF was examined in a 90-day oral toxicity study (Desert Labs, 2012b; Lynch et al., 2013b) according to OECD TG 408 (OECD, 1998) and following the principles of GLP. Sprague–Dawley rats (10/sex per group for the general toxicity phase and 10 females/group for the reproductive/developmental toxicity phase) were administered the NF (batch No Pm34901) by oral gavage at a dose of 0 (vehicle control), 100, 250 or 350 mg/kg bw per day for 90 days, followed by termination. Additional recovery groups (5 rats/sex per group) were assigned to receive the NF at doses of 0 or 350 mg/kg bw/day for 90 days and were sacrificed 28 days after cessation of the treatment. The doses were selected following a preliminary gavage dose-ranging trial. Gavage was selected because of the astringency and, therefore, potential satiety effects of the NF.

Findings related to body weight were predominant (Table 3) and were more pronounced in females than in males. Besides dose-related effects on body weight and body weight gain, also food consumption and food efficiency were lower compared to controls (statistically significant in females from a dose of 250 mg/kg bw per day and higher). Within the 4-week recovery period, food efficiency increased considerably, although the effects on body weight in the female animals were not completely reversible.

The applicant brought forward several arguments on why the effects on food consumption and on body weight observed in the study should not be considered as adverse. Dried *Hoodia*, and thus, the NF contains up to about 55% dietary fibres. The applicant provided studies with dietary fibre (sweet potato (*Ipomoea batatas*) tuber extract, cellulose, fructooligosaccharide, oat beta-glucan or apple pectin, hydroxypropylmethylcellulose, guar gum) that reported reductions in food uptake, body weight gain or fat mass in (obese) rats (Adam et al., 2014, 2015a,b; Brockman et al., 2014; Olubobokun et al., 2014). Reduced caloric intake or reduced body weight gain was associated with increases of satiety hormones, lowered insulin and glucose levels, increased levels of short-chain fatty acids in colon and caecum, thus providing some evidence for a possible mode of action of an effect of fibre on body weight. In addition, the applicant pointed out that there may be physical effects on the gastrointestinal tract due to the viscous nature of the NF that may lead to reduced food intake. The Panel notes that the above studies were performed with considerably higher doses of dietary fibre than those tested with the NF. In addition, there were no data provided on *Hoodia* to support these arguments. Effects of the NF on the palatability of the food are not plausible, as the test substance was administered via gavage. The Panel also notes that the feed used in the study contained 3% fibre and considers it unlikely that effects on bodyweight could be explained by the additional amount of fibre provided by the NF in addition to the consumption of fibre via the diet.

Effects on food consumption and body weight are sensitive markers of toxicity. The Panel, therefore, considers the lower food intake and body weights as potentially adverse.

Concomitant with effects on body weights, absolute organ weights were lower in female rats, statistically significant only for heart weights at 350 mg/kg bw per day. Relative adrenal and brain weights were higher in female rats at 250 mg/kg bw per day and above, relative kidney and liver weights were higher at 350 mg/kg bw per day. No treatment-related changes were found in the histopathological examinations of these organs. The Panel notes that increases in relative organ weights may be rather a result of the strongly reduced body weight than an organ-specific toxicological effect.

A dose-dependent increase in urine volume (statistically significant at 350 mg/kg bw per day) was observed in male and female rats (Table 3) with corresponding dose-dependent decreases in specific gravity (statistically significant at 350 mg/kg bw per day) and total protein in urine (statistically

significant in females administered 350 mg/kg bw per day). No analyses on consumption of drinking water were available. The Panel notes that these effects were quite pronounced and may indicate a general effect on fluid balance.

Table 3: Selection of findings of the 90-day oral toxicity study (Desert Labs, 2012b; Lynch et al., 2013b)

Parameter	Days of exposure	Sex	Dose (mg/kg bw per day)			
			0	100	250	350
Body weight (g)	92	M	557.9 ± 51.8	554.6 ± 56.6 (n = 9‡)	525.9 ± 29.3	521.2 ± 34.2 (n = 9‡)
		F	320.9 ± 26.3	324.3 ± 47.9	281.9 ± 25.7*	267.0 ± 22.3**
	92 + 28 recovery	M	620.2 ± 61.0	n.a.	n.a.	572.6 ± 68.2
		F	325.6 ± 22.7	n.a.	n.a.	290 ± 20.4*
Food consumption (g/day)	1–78[a]	M	29.71 ± 1.49	29.12 ± 2.25	27.92 ± 1.40	27.00 ± 1.67**
	1–92	F	20.66 ± 1.52	20.70 ± 1.92	18.32 ± 1.92*	16.48 ± 1.89***
	92 + 28 recovery	M	33.32 ± 8.70	n.a.	n.a.	30.79 ± 6.08
		F	21.22 ± 2.08	n.a.	n.a.	22.12 ± 2.15
Food efficiency (mg/kg/day)[b]	1–78[a]	M	0.137 ± 0.015	0.136 ± 0.017	0.130 ± 0.11	0.131 ± 0.008
	1–92	F	0.073 ± 0.009	0.072 ± 0.016	0.054 ± ±0.007**	0.053 ±0.007***
	92 + 28 recovery	M	0.036 ± 0.010	n.a.	n.a.	0.071 ± 0.015**
		F	0.009 ± 0.009	n.a.	n.a.	0.045 ± 0.018**
Heart W, abs. (g)	96	F	1.159 ± 0.208	1.100 ± 0.072	1.047 ± 0.149	0.944 ± 0.090**
Heart W, rel.			3.908 ± 0.825	3.648 ± 0.350	4.025 ± 0.431	3.870 ± 0.403
Heart W/ brain W			0.567 ± 0.132	0.526 ± 0.045	0.503 ± 0.075	0.458 ± 0.037*
Brain W, abs. (g)			2.064 ± 0.117	2.094 ± 0.096	2.082 ± 0.090	2.059 ± 0.064
Brain W, rel.	96	F	6.941 ± 0.547	6.986 ± 0.949	8.052 ± 0.708**	8.448 ± 0.585***
Adrenal W abs. (g)			0.0662 ± 0.0117	0.0777 ± 0.0105	0.0747 ± 0.0098	0.0702 ± 0.0092
Adrenal W, rel.	96	F	0.2230 ± 0.0453	0.2585 ± 0.0425	0.2877 ± 0.0330**	0.2885 ± 0.0463**
Adrenal W/ brain W			0.0321 ± 0.0052	0.0371 ± 0.0048	0.0359 ± 0.0048	0.0341 ± 0.0043
Kidney W abs. (g)			1.953 ± 0.233	2.152 ± 0.259	1.862 ± 0.151	1.847 ± 0.164
Kidney W, rel.	96	F	6.542 ± 0.564	7.103 ± 0.681	7.179 ± 0.516	7.568 ± 0.681**
Kidney W/ brain W			0.947 ± 0.103	1.027 ± 0.113	0.894 ± 0.060	0.897 ± 0.067
Liver W abs. (g)			7.805 ± 0.776	8.268 ± 0.865	7.446 ± 0.730	7.407 ± 0.740
Liver W, rel.	96	F	26.199 ± 2.440	27.281 ± 1.898	28.658 ± 1.973	30.362 ± 3.205**
Liver W/ brain Ws			3.781 ± 0.286	3.954 ± 0.443	3.573 ± 0.276	3.595 ± 0.310
Urine volume (mL)	93	M	6.5 ± 2.4	7.5 ± 2.1	8.3 ± 4.0	12.4 ± 6.7*
		F	5.5 ± 3.1	5.6 ± 1.6	7.9 ± 5.6	17.7 ± 7.7***
	114	M	7.1 ± 5.9	n.a.	n.a.	10.5 ± 10.1
		F	5.7 ± 3.7	n.a.	n.a.	4.1 ± 6.0
Urine, specific gravity	93	M	1.046 ± 0.012	1.039 ± 0.011	1.040 ± 0.014	1.030 ± 0.015*
	93	F	1.039 ± 0.018	1.034 ± 0.007	1.030 ± 0.010	1.014 ± 0.006*

Parameter	Days of exposure	Sex	Dose (mg/kg bw per day)			
			0	100	250	350
Protein in urine (mg/dL)	93	M	153 ± 39	143 ± 40	138 ± 53	128 ± 93
		F	52 ± 34	46 ± 11	35 ± 15	13 ± 5***

bw: body weight.
(a): No value available for day 1–92, food consumption was not measured during mating.
(b): Food efficiency = mean daily body weight gain/mean daily food consumption.
n.a. not assessed.
*p < 0.05, **p < 0.01, ***p < 0.001.
‡Two animals, one in the low-dose group (day 12) and one in the high-dose group (day 76), died due to gavage error.

The Panel notes apparent dose-related effects on body weight in the rats receiving the NF compared to controls (statistically significantly lower body weights in female rats in the mid- and high-dose groups). The Panel also notes apparent dose-related effects on urine volume (statistically significantly higher in the high-dose groups compared to controls). Therefore, the applicant was requested to subject the data to benchmark dose (BMD) modelling, taking into account the recommendations laid down in the guidance document of the EFSA Scientific Committee (2017).

In reply, the applicant submitted BMD analyses for data on body weight and urine volume using the EPA BMDS software (version 2.6) for the modelling. With regard to body weight, the applicant followed the recommendation of the EFSA Scientific Committee to use a 5% critical effect size (CES) (= benchmark response (BMR)). For urine volume, the applicant applied a BMR of 25%, the rationale being that given the much higher variability of urine volumes a BMR of 25% would account for a similar degree for the variability in the urine volume data as a BMR of 5% accounts for the variability in body weight data (i.e. about 0.4–0.7 SD). For both endpoints, body weight and urine volume, males and females were analysed separately.

Considering body weight, for male rats a $BMDL_{05}$ of 137.5 mg/kg bw per day was obtained, based on the 'recommended' model of the software. For female rats, the top-dose group was excluded because the BMDS software produced no 'viable' or 'recommended' model for either the assumption on non-constant variance or for constant variance. The applicant argued that this might be owing to the fact that the body weight of the female rats in the low-dose group was somewhat higher than those of the animals in the control group. Excluding the top-dose group, the Power model (not among those recommended in the Guidance of the EFSA Scientific Committee (2017)) yielded a $BMDL_{05}$ of 105 mg/kg bw per day for female rats. Considering urine volume, for male rats a $BMDL_{25}$ of 156.3 mg/kg bw per day was derived, based on a model which is not among those recommended in the above-mentioned guidance. Therefore, the applicant proposed instead the value generated by the 'Exponential model 3' of 118 mg/kg bw per day. The female data were not considered as useable by the software, irrespective of the exclusion of the top-dose group.

The Panel notes that for the endpoint 'body weight', the top-dose group of female rats was excluded from the BMD modelling provided by the applicant. For urine volume, no acceptable/'viable' model could be derived (for female rats). The Panel considers that it is not appropriate to exclude certain dose groups from the BMD analyses. The Panel also considers that it is particularly important to take into consideration data from the female rats, since the females have been shown to be more sensitive in the repeated-dose toxicity study.

Therefore, the Panel subjected the data on body weight and urinary volume from males and females to BMD modelling using the EFSA web tool for BMD analysis[5] which is based on PROAST, analysing the data from males and females in a combined data set analysis, with the factor 'sex' as a covariate. Confidence intervals (90%) were estimated around the BMDs and the corresponding values for the upper and lower confidence limits (BMDUs and BMDLs, respectively) were derived. Models could be fitted without the exclusion of any dose-group.

The lowest $BMDL_{05}$ of 53.5 mg/kg bw per day was obtained for body weight in female rats and is considered by the Panel as the reference point for the risk characterisation (for the BMD report see the Annex).

[5] https://efsa.openanalytics.eu/

3.8.4. Developmental and reproductive toxicity studies

In a combined reproductive and developmental toxicity screening study (Lynch et al., 2013b; Desert Labs, 2012b; described in 3.7.3.) according to OECD TG 422 (OECD, 1996), Sprague–Dawley rats (10 females/group) were administered the NF by oral gavage at doses of 0 (vehicle control), 100, 250 or 350 mg/kg bw per day from 11 weeks prior to mating, through mating and gestation and up to postnatal day 4. Dams and pups were sacrificed on postnatal day 4 and were assessed for body weight, food consumption and reproductive and developmental parameters. Reproductive endpoints included oestrus cycle, presence of conceptus, corpora lutea count, pre- and post-implantation loss, duration of gestation, maternal behaviour, litter size, number of live and stillborn pups and the presence of a milk band. Developmental endpoints included incidence of stillbirths, offspring sex ratio, pup weight and gross abnormalities of the thorax, abdomen, pelvis and palate.

Significantly lower body weights were noted in females receiving 250 or 350 mg/kg bw per day over gestational day (GD) 0–20. Significantly lower food consumption also was observed in females receiving 250 or 350 mg/kg bw per day during GD 0–7, which was accompanied by increased food efficiency.

No significant differences in the scores for the functional observational battery and motor activity tests were observed compared to controls. No apparent changes in oestrous cycle duration, evidence and time to mating, fecundity, gestation length, number of implantation sites, number of corpora lutea, pre- and post-implantation loss, litter weight, neonatal viability and sex ratio were observed compared to controls. All reproductive parameters recorded for treated dams were consistent with historical control ranges for Sprague–Dawley rats. No clinical or congenital findings in the F1 generation outside of the background incidence and type normally observed in the rat strain were observed in treated animals.

The no-observed-adverse-effect-level (NOAEL) for reproductive and developmental toxicity of the NF was determined to be 350 mg/kg bw per day, the highest dose tested, based on the lack of adverse effects on reproductive and developmental endpoints.

3.8.5. Human studies

The applicant provided two human studies (Lalazar et al., 2012; Landor et al., 2015).

The study by Lalazar et al. (2012) was an open-label, uncontrolled, single-centre study in patients suffering from non-alcoholic steatohepatitis (NASH). A preparation containing frozen slices of *H. parviflora* was administered daily to 10 patients with NASH for 30 days. In order to assess the extent to which the food used in the study is representative of the NF under evaluation, the applicant was requested to provide a full characterisation of the tested food. The applicant replied that the full characterisation and properties of the tested food were not available to the applicant as the applicant did not conduct the study nor prepare the food tested in the study. The Panel notes that the study was an uncontrolled, open-label intervention, and that it is unclear to which extent the food used in the study is representative of the NF under evaluation. The Panel considers that no conclusions can be drawn from this study for the safety assessment of the NF.

A randomised, single-blind, placebo-controlled, three-arm weight-loss study (Landor et al., 2015) was conducted in subjects of various body weight (i.e. normal weight, overweight, obese, 'very obese'). The test food was administered in the form of frozen cubes. The applicant provided further details of the test food such as the proximate analysis and its dry weight. The applicant also provided the content of the hoodigosides, which were within the specifications as set for the NF. The doses administered were equivalent to 142.5 mg dried aerial parts of *Hoodia parviflora* (i.e. the NF) per cube. A total of 204 subjects were randomised to receive: (i) two frozen cubes per day for 10 days followed by one frozen cube for the next 30 days (n = 79 subjects); (ii) one frozen cube per day for 40 days (n = 79 subjects) or (iii) a placebo (n = 46 subjects). The study participants' BMI, which differed considerably (i.e. from 19.7 to 47 kg/m^2) among the subjects, was not taken into account for the randomisation (i.e. no stratification was applied). The randomisation was performed by asking the subjects to randomly choose 'day one' to begin the trial and by assigning the subjects to the study groups according to the date chosen, which resulted in an imbalanced design (i.e. with the placebo group having fewer participants than the two Hoodia groups). A total of 101 subjects withdrew from the study, corresponding to an overall drop-out rate of 49%. The Panel notes the methodological weaknesses of the study (i.e. randomisation based on participants' choice of starting date, no stratification of the heterogeneous study group). The Panel also notes the high risk of (selection) bias owing to the high drop-out rate (i.e. half of the participants). The Panel considers that no conclusions can be drawn from this study for the safety assessment of the NF.

3.9. Allergenicity

The protein content of the NF can be up to 4.5%. The applicant provided an enzyme-linked immunosorbent assay (ELISA) screening, which did not reveal cross-reactivity with some of the major food allergens, i.e. peanuts, milk, egg, crustacean, soy bean or with gluten. Upon request by a MS, the applicant conducted a literature search using the electronic search tool Proquest Dialog™ to identify cases of food allergenicity among the species of the Apocynaceae family, the taxonomic family to which *H. parviflora* belongs. While cases of allergenicity via inhalation were observed for some species of the Apocynaceae family, no cases of food allergy were identified for any species of the Apocynaceae family through the literature search.

The applicant also indicated that the NF is being marketed in the USA since 2011 and that there have been no reports of allergic reactions to the NF.

The Panel considers that the risk of allergic reactions to the NF is low.

4. Discussion

The NF is the whole dried aerial parts of *Hoodia parviflora*, which is a succulent cactus-like milkweed plant native to southern Africa.

The information provided on the composition, specifications, the production process, batch-to-batch variability and the stability of the NF is sufficient.

The applicant intends to use the NF in a number of energy-reduced/sugar-free/no-added-sugar foods in quantities of up to 15 mg per serving. The applicant also proposes to provide the NF as a food supplement, with a recommended daily dose of up to 40 mg/day. The target population proposed by the applicant is adults.

When estimating intakes of the NF from the foods intended to be fortified with the NF, the highest intakes were found for elderly individuals, with mean and high (95 percentile) intakes of 0.3 and 1.0 mg/kg bw per day, respectively.

The Panel notes that no information on ADME of the NF was provided.

One 90-day repeated dose oral toxicity study in rodents was provided with the NF, which was administered at doses of 100, 250 and 350 mg/kg bw per day. When the data from the study were subjected to BMD modelling, a BMD lower confidence limit ($BMDL_{05}$) of 53.5 mg/kg bw per day (for the endpoint bodyweight) was derived, which is considered by the Panel as the reference point.

As indicated earlier (Section 3.8), the Panel notes that the batch tested in the toxicity study contained more than four times less total hoodigosides than the maximum level as set in the specifications, which adds to the uncertainty.

Considering the $BMDL_{05}$ of 53.5 mg/kg bw per day, and the estimated high intakes of the NF from fortified foods of 1.0 mg/kg bw per day, the resulting margin of exposure (MoE) is 53.5. With regard to food supplements and the proposed maximum daily intake of the NF of 0.57 mg/kg bw per day, the resulting MoE is 94. The Panel considers these MoEs for fortified foods and food supplements as insufficient.

Considering the $BMDL_{05}$ of 53.5 mg/kg bw per day and by applying an uncertainty factor of 400 (composed of a factor of 100 to account for inter- and intra-species variability plus a factor of 4 to account for uncertainty for the content of the hoodigosides tested in the 90-day toxicity study), the Panel considers an intake of 0.134 mg/kg bw per day of the NF in the form of food supplements as safe. In adults (i.e. the target population) with a default body weight of 70 kg, this intake level corresponds to a maximum dose of 9.4 mg/day.

The Panel considers that an additional safety factor of 2 for extrapolation from subchronic to chronic exposure was not necessary, as effects on body weight and feed intake noted in the short-term study did not increase further in the 90-day study at comparable doses and were reversible.

5. Conclusions

The Panel concludes that the addition of the NF, dried aerial parts of *Hoodia parviflora*, to foods as a food ingredient at the uses and use levels as proposed by the applicant would exceed intake levels considered safe in humans.

The Panel considers that the NF is safe to be used as a food supplement at a maximum dose of 9.4 mg/day. The target population is adults.

Steps taken by EFSA

1) Letter from the European Commission to the European Food Safety Authority with the request for a scientific opinion on the safety of dried aerial parts of *Hoodia parviflora*. Ref. Ares(2016)389215, dated 25 January 2016.
2) On 28 January 2016, EFSA received the following documentation: dossier 'Final_EU_Novel_Foods_Dossier_for_Hoodia_confidential', submitted by Desert Labs Ltd, Israel; initial assessment report (i.e. 'Safety Assessment of Dried Aerial Parts of Hoodia parviflora (DHP)' (Ref. Ares(2015)3550322 - 28/08/2015)) carried out by the Food Safety Authority of Ireland; Member States' comments and objections; responses by the applicant to the initial assessment report and to the Member States' comments and objections.
3) On 23 February 2016, EFSA requested the applicant to provide missing information.
4) On 11 March 2016, EFSA received the missing information as submitted by the applicant.
5) The application was considered valid as of 6 April 2016.
6) On 22 September 2016, EFSA requested the applicant to provide supplementary information to accompany the application.
7) Additional data were provided by the applicant on 4 and 7 November 2016.
8) On 6 December 2016, EFSA requested the applicant to provide supplementary information to accompany the application.
9) Additional data were provided by the applicant on 14 December 2016.
10) On 23 February 2017, EFSA requested the applicant to provide supplementary information to accompany the application.
11) Additional data were provided by the applicant on 28 April 2017.
12) On 1 June 2017, EFSA requested the applicant to provide supplementary information to accompany the application.
13) Additional data were provided by the applicant on 21 June 2017.
14) During its meeting on 20 September 2017, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of the dried aerial parts of *Hoodia parviflora* as a NF pursuant to Regulation (EC) No 258/97.

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
ALT	alanine aminotransferase
AOAC	Association Of Analytical Communities
AOCS	American Oil Chemists' Society
AST	aspartate aminotransferase
BAM	Bacteriological Analytical Manual
BMD	benchmark dose
BMR	benchmark response
Bw	body weight
CES	critical effect size
CFU	colony forming unit
CMMEF	Compendium of Methods for the Microbiological Examination of Foods
ELISA	enzyme-linked immunosorbent assay
EPA	Environmental Protection Agency
FDA BAM	Food and Drug Administration Bacteriological Analytical Manual
GD	gestational day
GLP	Good Laboratory Practice
GM	genetically modified
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis Critical Control Points
LC–MS/MS	liquid chromatography with tandem mass spectrometry

MGHPB	Health Products and Food Branch of Health Canada methods for the microbiological analysis of foods
MoE	Margin of Exposure
MS	Member State
MWD-ICP-MS	multiple wavelength detector-inductively coupled plasma-mass spectrometry
NASH	non-alcoholic steatohepatitis
NCFA	Nordic Committee on Food Analysis
NOAEL	no-observed-adverse-effect-level
NF	novel food
OECD	Organisation for Economic Co-Operation and Development
SI	Standards of Israel
TG	Test Guideline
UPLC/MS	ultra-performance liquid-chromatography/mass spectrometry

Annex – Benchmark Dose Modelling Report

Data description

The endpoint to be analysed is body weight.
Data used for analysis:

Dose	Body weight	SD	n	Sex
0	320.9	26.3	10	f
100	324.3	47.9	10	f
250	281.9	25.7	10	f
350	267.0	22.3	10	f
0	557.9	51.8	10	m
100	554.6	56.6	9	m
250	525.9	29.3	10	m
350	521.2	34.2	9	m

Software used

Results are obtained using the EFSA web-tool for BMD analysis.
Fitting benchmark dose models is based on the R-package PROAST, version 64.8.

Results

Response variable: body weight

Fitted Models

Model	Converged	loglik	npar	AIC
Full	Yes	78.26	9	−138.52
Full-v	Yes	79.53	10	−139.06
m1-v	Yes	4.47	3	−2.94
m1-av	Yes	66.58	4	−125.16
Expon. m3-v	Yes	7.10	5	−4.20
Expon. m3-av	Yes	75.70	6	−139.40
Expon. m3-abv	Yes	78.81	7	−143.62
Expon. m5-av	Yes	76.20	7	−138.40
Expon. m5-abv	Yes	79.02	8	−142.04
Hill m3-av	Yes	75.72	6	−139.44
Hill m3-abv	Yes	78.84	7	−143.68
Hill m5-av	Yes	76.19	7	−138.38
Hill m5-abv	Yes	79.01	8	−142.02

Estimated Model Parameters

EXP

estimate for var-f: 0.010059
estimate for var-m: 0.005907
estimate for a-f: 323.809372
estimate for a-m: 555.209302
estimate for CED-f: 136.601069
estimate for CED-m: 276.734706
estimate for d-: 1.466559

HILL

estimate for var-f: 0.010039
estimate for var-m: 0.005909
estimate for a-f: 323.822832
estimate for a-m: 554.964018

estimate for CED-f: 137.171074
estimate for CED-m: 278.881228
estimate for d-: 1.554992

Final BMD Values

Model	Subgroup	BMDL	BMDU	BMD
Expon. m3-abv	f	53.5	228	140
Expon. m3-abv	m	151.0	717	280
Hill m3-abv	f	55.0	227	140
Hill m3-abv	m	154.0	701	280

Lowest BMDL and highest BMDU Values

Subgroup	BMDL.lowest	BMDU.highest
f	53.5	228
m	151	717

Visualisation